B4

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 October 2003 (23.10.2003)

PCT

(10) International Publication Number
WO 03/086349 A1

(51) International Patent Classification[7]: A61K 9/12, 9/70, 31/58, 31/167, 47/10, 47/26

(21) International Application Number: PCT/US03/10285

(22) International Filing Date: 1 April 2003 (01.04.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0207899.6 5 April 2002 (05.04.2002) GB

(71) Applicant *(for all designated States except US)*: **3M INNOVATIVE PROPERTIES COMPANY** [US/US]; 3M Center, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **OLIVER, Martin, J.** [GB/GB]; 37 St. Leonards Road, Clarendon Park, Leicestershire LE2 1WS (GB). **JINKS, Philip, A.** [GB/GB]; 41 Highfields Drive, Loughborough, Leicestershire LE11 3JS (GB).

(74) Agents: **RINGSRED, Ted, K.** et al.; Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

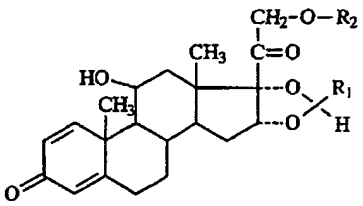
(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: FORMOTEROL AND CICLESONIDE AEROSOL FORMULATIONS



(I)

(57) Abstract: A pharmaceutical aerosol formulation comprising particles of formoterol or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, said particles being suspended in the formulation; a compound of the formula (I), in which: R_1 is 1-butyl, 2-butyl, cyclohexyl or phenyl and R_2 is acetyl or isobutanoyl, said compound of formula (I) being dissolved in the formulation; and a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof.

WO 03/086349 A1

FORMOTEROL AND CICLESONIDE AEROSOL FORMULATIONS

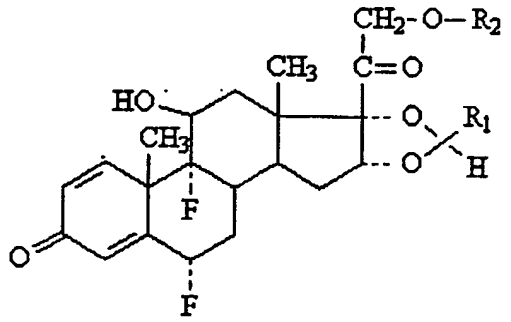
Field of the Invention

This invention relates to medicinal aerosol formulations and in particular to aerosol formulations containing formoterol in suspension and ciclesonide in solution suitable for administration to the respiratory tract.

Background

Formoterol, N-[2-hydroxy-5-(1-hydroxy-2-((2-(4-methoxyphenyl)-1-methylethyl) amino)ethyl) phenyl] formamide, particularly in the form of its fumarate salt, is a bronchodilator used in the treatment of inflammatory or obstructive airways diseases.

GB-2247680 discloses pregna-1,4-diene-3,20-dione-16-17-acetal-21 esters and their use in the treatment of inflammatory conditions. The compounds have the general structure:



wherein R_1 is 2-propyl, 1-butyl, 2-butyl, cyclohexyl or phenyl; and R_2 is acetyl or isobutanoyl. Ciclesonide is 11β, 16α, 17, 21-tetrahydroxypregna 1,4-diene-3,20-dione, cyclic 16,17-acetal with cyclohexanecarboxaldehyde, 21-isobutyrate having the structure of general formula given above without fluorine atoms and in which

R_1 is cyclohexyl and R_2 is isobutanoyl.

DE 19541689 discloses the combined use of ciclesonide with a β2-sympathomimetic, for the treatment of respiratory disorders. It is stated that such combinations are suitable for long-term therapy and provide good local and anti-inflammatory effect in conjunction with quick relief of bronchospasms and without systemic side effects. As an exemplary formulation, DE 19541689 discloses a suspension aerosol composition consisting of ciclesonide (3.7 g) and formoterol fumarate dihydrate (1.1g) as micronized particles dispersed in trichlorofluoromethane (1.99 kg), dichlorodifluoromethane (3.00 g) with sorbitan trioleate (15.5 g).

However at the time of the filing of DE 19541689 in 1995, these chlorofluorocarbon (CFC) propellants were generally understood to provoke the degradation of stratospheric ozone. Thus there was at that time and there still is a general need to provide aerosol formulations for medicaments, which employ so-called "ozone-friendly" propellants. A class of propellants which are believed to have minimal ozone-depleting effects in comparison to conventional CFCs comprise hydrofluorocarbons, in particular 1,1,1,2-tetrafluoroethane ("HFA 134a") and 1,1,1,2,3,3,3-heptafluoropropane ("HFA 227"). A number of medicinal aerosol formulations using such propellant-systems are disclosed in, for example, EP 0372777, W091/04011, W091/11173, W091/11496, W091/14422, EP 0 504 112, W093/11745, WO 93/11747, WO 97/47286 and WO 98/52542 (all hereby incorporated by reference). These applications are all concerned with the preparation of pressurised aerosols for the administration of medicaments and seek to overcome problems associated with the use of this new class of propellants, in particular the problems of stability associated with the pharmaceutical formulations prepared.

EP-A-0504112, for example, discloses a pharmaceutical composition for aerosol use containing: (a) a liquefied propellant gas or propellant gas mixture with a vapor pressure exceeding 1 bar but less than 6 bar (20°C) from the unsubstituted

or partially to completely fluorinated hydrocarbon group; (b) a non-ionic tensile of the monoacetylated or diacetylated monoglyceride group;(c) a pharmaceutical active substance or combination of active substances, and, if necessary,(d) other common pharmaceutical accessory substances suitable for aerosol formulations. It is stated the basic purpose of that invention was to find a special accessory suspending substance for active substances in aerosol formulations, which dissolves better in liquefied "alternative" propellant gases than the accessory suspending substances hitherto recognized and used. It is stated that surprisingly, it was discovered, in solving this problem, that non-ionic tensides of the monoacetylated or diacetylated monoglyceride group are very soluble in the "alternative" propellant gases mentioned, particularly in HFA 227, are beneficial to the production of homogenous suspensions, and also have outstanding metering valve lubrication properties. Some of the examples of EP-A-0 504 112 disclose formulations comprising formoterol fumarate.

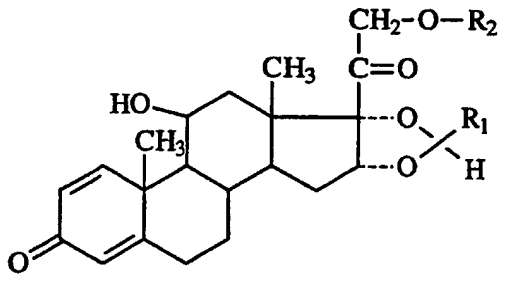
WO 93/11747 discloses a pharmaceutical suspension formulation suitable for aerosol administration, consisting essentially of a therapeutically effective amount of a drug and a propellant selected from the group consisting of HFA 134a, HFA 227, and a mixture thereof, the formulation being further characterized in that it exhibits substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period, is substantially and readily redispersible, and upon redispersion does not flocculate so quickly as to prevent reproducible dosing of the drug. The application specifically discloses formulations of formoterol fumarate in HFA 134a, HFA 227 and 1:1 mixtures of HFA 134a and HFA 227. The formulations do not contain surfactants or ethanol. It is stated that mixtures of HFA 134a and HFA 227 may be adjusted for density matching with the drug.

WO 93/11745 discloses pharmaceutical aerosol formulations, substantially free of surfactant containing fluorocarbon or hydrogen-containing chlorofluorocarbon propellants and up to 5% of a polar co-solvent. Preferred propellants are HFA 134a and HFA 227 which are preferably used alone. The preferred polar co-solvent is ethanol and it is stated that in general only small quantities e.g. 0.05 to

3.0% w/w of polar co-solvent are required to improve the dispersion and the use of quantities in excess of 5% w/w may disadvantageously tend to dissolve the medicament.

WO 97/47286 discloses a pharmaceutical suspension formulation suitable for aerosol administration, consisting essentially of: (a) from 0.0025 to 0.1% w/w of micronized formoterol, or an acid addition salt thereof and (b) from 0.1 to 5.0% w/w ethanol, (c) HFA 134a, HFA 227 or a mixture of HFA 227 and HFA 134a and optionally (d) a surfactant other than a monoacetylated or diacetylated monoglyceride, the formulation being further characterized in that it exhibits substantially no growth in particle size or change in crystal morphology of the drug over a prolonged period, is substantially and readily redispersible, and upon redispersion does not flocculate so quickly as to prevent reproducible dosing of the drug. The application specifically discloses formulations comprising formoterol fumarate dispersed in HFA 134a, HFA 227 or mixtures thereof and 1 to 3% ethanol. It is stated that it is important to ensure the formoterol fumarate does not come into contact with high concentrations e.g. above 10% w/w, of ethanol since the drug would dissolve leading to instability and crystal growth problems in the final formulation and that the maximum concentration of ethanol during formulation is preferably less than 5%. It is stated that aerosol compositions consisting of formoterol fumarate, HFA 134a and ethanol have proved to be extremely sensitive to ethanol concentration and an ethanol concentration of 3.5% w/w may cause unacceptable crystal growth.

WO 98/52542 discloses a pharmaceutical compositions comprising a therapeutically effective amount of a compound of the formula (I):



in which: R_1 is 1-butyl, 2-butyl, cyclohexyl or phenyl and R_2 is acetyl or isobutanoyl, and a hydrofluorocarbon propellant, preferably selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof, and cosolvent, preferably ethanol, in an amount effective to solubilize the compound of formula (I) and optionally a surfactant. The application specifically discloses solution formulations comprising ciclesonide (1 to 5 mg/ml) in HFA 134a, HFA 227 or mixtures of HFA 134a and HFA 227 and 5 to 20% by weight ethanol.

Despite the various approaches used in formulating drugs for use in aerosol inhalation, a number of serious difficulties and uncertainties are still often encountered in attempting to develop a physically and chemically stable CFC-free formulation that reliably delivers an accurate dose of drug having the proper particle size range.

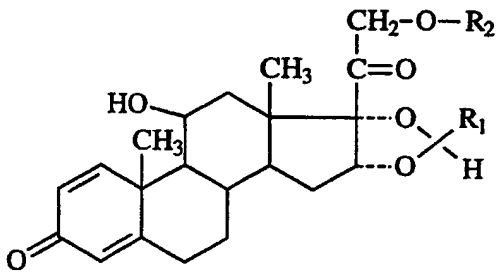
Summary of the Invention

There is a need for a CFC-free medicinal aerosol product containing formoterol and ciclesonide (or similar molecules) that is chemically and physically stable and that is suitable for delivery to the respiratory system of a patient.

Surprisingly it has been found that it is possible to provide physically and chemically stable formulations of formoterol fumarate in suspension and

ciclesonide in solution at therapeutic effective concentrations in HFA 134a and/or HFA 227 propellant.

Accordingly in one aspect of the present invention there is provided a pharmaceutical aerosol composition comprising
particles of formoterol or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, said particles being suspended in the formulation;
a compound of the formula (I):



in which: R_1 is 1-butyl, 2-butyl, cyclohexyl or phenyl and R_2 is acetyl or isobutanoyl, said compound of formula (I) being dissolved in the formulation; and a propellant selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane and a mixture thereof.

WO 99/28296 and WO 99/65464 disclose medicinal aerosol formulations comprising a first drug suspended in propellant and a second drug dissolved in the formulation. However, ciclesonide or a similar molecule is not disclosed as a drug in either document, formoterol is not disclosed in WO 99/65644, and neither document discloses such a formulation containing formoterol or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and a compound of formula (I).

Due to the reported sensitivity of particulate formoterol, in particular formoterol fumarate, dispersed in HFA 134a and/or HFA 227 propellant to ethanol, it was

considered not feasible to formulate particulate formoterol in combination with therapeutically effective amounts of ciclesonide (or similar molecules) at levels of ethanol that would be needed for complete dissolution of ciclesonide (or similar molecules).

Surprisingly, it was found possible to successfully formulate the drug combination at levels of ethanol considered unsuitable for one of the drugs. In particular, it was found that ethanol can be present in an amount effective to completely solubilize a compound of formula (I), such as ciclesonide, yet without the formoterol or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, such as formoterol fumarate, exhibiting detrimental growth in particle size or change in crystal morphology over a high stress storage interval.

The amount of ethanol in the formulation is advantageously present in a amount from 3 to 20% by weight, preferably from 3.5 to 12% by weight, more preferably from 3.5 to 10 % by weight, even more preferably from 5 to 10 % by weight, most preferably from 5 to 8% by weight.

Preferably the propellant comprises HFA 134a, more preferably HFA 134a is applied as the only propellant component.

To further enhance physical stability and homogeneity of the dispersion of formoterol or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof, the formulations may advantageously comprise a particulate bulking agent having a mass median diameter of less than one micron.

Formulations according to the invention are particularly suitable for use in inhalation therapy, in which a therapeutically effective amount of the formulation is delivered to the lung by oral or nasal inhalation, more particularly for prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated. The present invention also

provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist and/or antiinflammatory corticosteroid is indicated, which comprises administration via inhalation a therapeutically effective amount of the formulation as described above. In particular, the present invention provides such methods for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

In another aspect of the present invention, there is provided a dispenser comprising an aerosol vial equipped with a dispensing valve containing a formulation as described above.

Detailed Description

It is to be understood that the present invention covers all combinations of particular and preferred aspects of the invention described herein.

As would be appreciated by the skilled person, formoterol includes two asymmetric centres. The present invention includes each isomer of formoterol either in substantially pure form or admixed in any proportions or a racemic mixture, particularly the (R, R)-isomer. The enantiomers of formoterol have been described previously, for example, in WO 98/21175 and US5795564.

By the term "physiologically functional derivative" is meant a chemical derivative of formoterol having the same physiological function as the free compound, for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids. Pharmaceutical acceptable acid addition salts include but are not limited to those formed from hydrochloric, hydrobromic, sulphuric, citric,

tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic, isethionic, and naphthalenecarboxylic, such as 1-hydroxy-2-naphthalenecarboxylic acids.

Pharmaceutically acceptable esters of formoterol may have a hydroxyl group converted to a C_{1-6} alkyl, aryl, aryl C_{1-6} alkyl, hetaryl (such as furanyl) or amino acid ester.

In preferred embodiments of the invention, formoterol fumarate (suitably as in the form of the dihydrate) is applied in combination with the compound of formula (I).

The compound of formula (I) is preferably ciclesonide.

Hereinafter, the term "formoterol " is understood to include formoterol or a pharmaceutical acceptable salt, solvate, or physiologically functional derivative thereof, preferably formoterol fumarate, more preferably formoterol fumarate dihydrate, while the term "compound of formula (I)" includes preferably ciclesonide.

Formoterol and the compound of formula (I) are generally present in a formulation of the invention in a therapeutically effective amount.

The amount of formoterol and compound of formula (I), which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the subject under treatment, and the particular disorder or disease being treated. Suitably, the pharmaceutical formulations which are suitable for inhalation according to the invention comprise formoterol and a compound of formula (I) in amounts such that one or two actuations provide a therapeutically effective dose, for example, a dose of formoterol of 1 mcg to 50 mcg, preferably 3 mcg to 25 mcg, more preferably 4 mcg to 12 mcg and a dose of the compound of Formula (I) of 20 mcg to 1 mg, preferably 35 mcg to 500 mcg, more preferably, 50 mcg to

200 mcg. Various dosing of the individual drugs can be advantageously combined for particular disorders or subjects under treatment.

Preferably formoterol constitutes about 0.06 to about 0.60 mg per ml, more preferably about 0.08 to about 0.30 mg per ml, most preferably about 0.10 to about 0.20 mg per ml of the formulation.

The particles of formoterol are generally micronised particles or particles processed by other methods, preferably having a mass median diameter equal to or greater than 1 micron, more particularly from 1 to 10 micron, even more particularly from 1 to 5 micron. Smaller particles having a mass median diameter of less than one micron may also be suitable.

The compound of formula (I) is generally present at a concentration of from about 0.5 to about 8 mg per ml, preferably about 1 to about 5 mg per ml, most preferably about 1 to about 4 mg per ml of the formulation.

The formulations of the invention typically comprise an adjuvant to aid the complete dissolution of the compound of formula (I). The level of adjuvant is desirably selected such that the compound of formula (I) is completely soluble in the aerosol formulation over the temperature range likely to be encountered by the product during use, e.g. 10 to 35°C, while the suspended formoterol exhibits substantially no growth in particle size (e.g. a growth of 25% or less (e.g. based on mass median diameter as determined by laser diffraction) after high stress cycling (i.e. 4 temperature cycles in a 24 hour period, where one cycle is defined as: 4°C at a duration of 2 h; ramping up from 4 to 40°C in 1 h; 40°C for 2 h and ramping down from 40 to 4°C in 1 h) over a period of 10 days). Suitable adjuvants are disclosed in EP-A-0372777. Ethanol is a preferred adjuvant. When ethanol is applied as adjuvant, it has been found that ethanol is desirably present in an amount from 3 to 20% by weight, preferably from 3.5 to 12% by weight, more preferably from 3.5 to 10 % by weight, even more preferably from 5 to 10 %, most preferably from 5 to 8% by weight of the formulation.

The propellant is selected from HFA 134a, HFA 227 and mixtures thereof. Preferably the propellant comprises HFA 134a, either in a mixture with HFA 227 or more preferably as the only propellant component. Variation of the concentration of HFA 134a and HFA 227 in mixtures allows adjustment of the density of the propellant to match the density of the suspended formoterol. Density matching may decrease the rate of sedimentation or creaming of the suspended formoterol particles.

For formulations comprising ethanol as adjuvant and HFA 134a and/or HFA 227 as propellant, it has been observed that the desired level of ethanol may vary in relation to the particular selection of propellant. Surprisingly, such formulations including HFA 134a as the only propellant demonstrate superior performance "over HFA 227 only formulations", e.g. enhanced stability of suspended formoterol particles, although such formulations typically require higher levels of ethanol for the complete dissolution of the compound of formula (I) e.g. over a temperature range of 10 to 35 °C (in comparison to formulations with HFA 227 as the only propellant). Further, it has been surprisingly found that for formulations with HFA 134a as the only propellant component and containing concentrations of the compound of formula (I), such that a level of ethanol of less than 5 % by weight may be sufficient to completely dissolve said compound e.g. over a temperature range of 10 to 35°C, the application of higher levels of ethanol (5 % or more) is advantageous, in that such formulations show superior uniformity in through life content testing and/or superior results in loss in dose testing for both the compound of formula (I) and formoterol.

The aerosol formulations of the invention may preferably contain surfactant, more preferably a surfactant other than a monoacetylated or diacetylated monoglyceride, for e.g. imparting a flocculant effect for the suspended formoterol, which may allow less migration of the drug to and from the metering chamber. When surfactant is included in a formulation it is generally present in an amount of about 0.001 % to 0.010 % by weight of the formulation. Suitable surfactants are well known in the art and include sorbitan trioleate, oleic acid and

lecithin. Surfactants, such as oligolactic acid derivatives disclosed in WO94/21228 and WO94/21229, and other surfactants disclosed in the literature may be used. As a surfactant oleic acid is preferred. The formulations are preferably free of other excipients.

It has been found that a bulking agent having a mass median diameter of less than one micron may be applied to enhance physical stability and homogeneity of the suspension of the formoterol particles. It is not necessary for the surface of the bulking agent or the drug to be coated with a surface modifier to achieve improved stability. In particular it has been found that the application of such a nano-sized bulking agent aids in minimizing the tendency of formoterol to cream or sediment, depending on the density difference of the drug and the propellant. More particularly, it has been found that the application of such a nano-sized bulking agent aids in maintaining a high sediment volume (i.e. minimizing a dense packing of the sediment) and/or the formation of a voluminous, loosely flocculated matrix, enhancing the re-dispersion and/or de-flocculation of the drug upon agitation.

The mass median diameter of the bulking agent can advantageously be as low as 300 nanometers, more desirably as low as 250 nanometers, even more desirably the mass median diameter is in the range of 100 to 250 nanometers and most desirably in the range of 150 to 200 nanometers.

Mass median diameter (which is equivalent to volume median diameter) can be determined using any conventional particle size measurement method known to those skilled in the art. Suitable methods include for example laser diffraction, photon correlation spectroscopy (e.g. using a spectrometer available under the trade designation Brookhaven PCS from Brookhaven Inc.), spinning disc centrifuging (using an instrument available under the trade designation CPS Disc Centrifuge from Chemical Process Specialists Inc.) and scanning electron microscopy (SEM). Mass median diameter is preferably determined by laser diffraction, photon correlation spectroscopy or spinning disc centrifuging, more

preferably by laser diffraction, more particularly laser diffraction using an analyser available under the trade designation Malvern Mastersizer 2000 laser light diffraction particle size analyser from Malvern Instruments Ltd.

Preferred bulking agents include lactose, DL-alanine, ascorbic acid, glucose, sucrose D(+)trehalose as well as their various hydrates, anomers and/or enantiomers. Lactose including its various forms, such as α-lactose monohydrate and β-lactose and alanine are more preferred. Lactose, in particular in its α-lactose monohydrate form, is most preferred as a bulking agent due to e.g. processing considerations. Other suitable bulking agents include other saccharides e.g. D-galactose, maltose, D(+)raffinose pentahydrate, sodium saccharin, polysaccharides e.g. starches, modified celluloses, dextrins or dextrans, other amino acids e.g. glycine, salts e.g. sodium chloride, calcium carbonate, sodium tartrate, calcium lactate, or other organic compounds e.g. urea or propyliodone.

Based on the amount of formoterol in the formulation, the weight ratio of formoterol to bulking agent is generally in the range 1:0.1 to 1:25, preferably 1:2 to 1:15, even more preferably 1:4 to1:12 and most preferably about 1:10.

The bulking agent may be reduced to the required particle size by any convenient method, e.g. grinding, air-jet milling etc. Preferably the bulking agent is reduced to nanoparticle size in a high pressure homogenizer, such as the commercially available Avestin Emulsiflex homogenizers and the Microfluidics Microfluidizer homogenizers. In the processing with high pressure homogenizers, certain bulking agents can be reduced to the desired particle size using lower pressures than that applied for other bulking agents. For example, it has been found that lactose, more specifically α-lactose monohydrate, can be effectively reduced to the desired particle size using pressures between about 10,000 and about 21,000 psi, while for effective particle size reduction of alanine or sucrose higher pressures of about 25,000 psi for repeated passes were applied.

The bulking agent may be prepared in a slurrying aid which is a low volatility solvent such as ethanol. It may be prepared in a slurrying aid which is a component of the final aerosol formulation, or it may be prepared in a solvent that is subsequently removed or exchanged with a component of the formulation by some process such as centrifugation and decanting, dialysis, evaporation etc.

It is particularly convenient to use a slurrying aid in the high pressure homogenizer which is a low volatility component of the aerosol formulation and after particle size reduction has been achieved the slurry may be adjusted if necessary, e.g. concentrated by centrifugation, decanting etc. Whilst it has been found that slurries with excessively high powder loadings may be difficult to process due to their rheological properties, it is generally advantageous to process slurries with powder loading concentrations which approach this processing limit in order to achieve the desired particle size distribution in the shortest processing time. Thus, the weight ratio of liquid:solid is generally in the range 5:1 to 100:1, preferably 5:1 to 20:1, and most preferably about 8:1 to about 10:1.

The present invention also provides a method of preparing a formulation according to the invention, the method comprising the steps of (i) providing a solution of the compound of formula (I) in HFA 134a and/or HFA 227 and (ii) dispersing particles of formoterol in the solution. For formulations containing adjuvant, in particular ethanol, typically step (i) includes sub-steps of mixing the compound of formula (I), and if applicable surfactant, in an appropriate amount of adjuvant and adding the resultant to an appropriate amount of HFA 134a and/or HFA 227 in liquid form (chilled to below its boiling point or range). Step (ii) typically includes the following sub-steps: removing a portion of the compound of formula (I) containing solution, adding particulate formoterol to this portion to form a formoterol-containing slurry, mixing the formoterol-containing slurry, preferably after high shear mixing thereof, in the remaining portion of the original compound of formula (I) containing solution.

For formulations containing a nano-sized bulking agent, a preferred method of preparing a formulation comprises the steps of (i) forming a slurry of bulking agent with a component of the formulation; (ii) subjecting the slurry to high pressure homogenization; and (iii) combining the resulting slurry with other components of the aerosol formulation. For formulations containing ethanol, the slurry of bulking agent may be advantageously prepared with an appropriate amount of ethanol. The slurry is subjected to high pressure homogenization prior to adding it to the remainder of the formulation. During manufacture, typically the slurry of bulking agent is then added to a solution of the compound of formula (I) in an appropriate amount of HFA 134a and/or HFA 227 and, if applicable an appropriate amount of adjuvant (e.g. ethanol) and/or surfactant. (Said solution prepared in a similar manner as described above.) In a subsequent step, particles of formoterol are then dispersed in compound of formula (I) containing liquid. As described above, this is typically achieved by taking off a portion of the compound of formula (I) containing liquid, in an intermediate step, and adding particulate formoterol to this portion to form a slurry of formoterol. This formoterol slurry, typically after high shear mixing thereof, is then re-added and mixed with the remaining portion of the original compound of formula (I) mixture.

Dispensers comprising an aerosol vial equipped with conventional dispensing valves, preferably metered dose valves, can be used to deliver formulations of the invention. Conventional dispensers and aerosol vials can be used to contain a formulation of the invention. However certain vials may enhance the chemical stability of certain formulations of the invention. Therefore it is preferred to contain a formulation of the invention within a glass aerosol vial or a metal, in particular aluminum, vial having an interior surface coated with a polymer, in particular a fluorocarbon polymer. Advantageously other internal surfaces, in particular such surfaces of components of the valve, or all of the internal surfaces of the dispenser may be also coated with a coating comprising a polymer, in particular a fluorocarbon polymer. Suitable fluorocarbon polymers include fluorocarbon polymers, which are made of multiples of one or more of the following monomeric units: tetrafluoroethylene (PTFE), fluorinated ethylene propylene (FEP),

perfluoroalkoxyalkane (PFA), ethylene tetrafluoroethylene (ETFE), vinylidenefluoride (PVDF), and chlorinated ethylene tetrafluoroethylene. Polymers, which have a relatively high ratio of fluorine to carbon, such as perfluorocarbon polymers e.g. PTFE, PFA, and FEP, are preferred; FEP is particularly preferred.

The valve may be any suitable metering valve with an outlet made from, for example stainless steel, acetal, nylon or polybutylene terephthalate and with seals made from nitrile or EPDM elastomer.

A formulation of the invention can be administered to the lung by oral or nasal inhalation. Oral inhalation is preferred, and conventional actuators for oral inhalation can be used in connection with a formulation of the invention. Good respirable doses can be achieved with an orifice diameter within the range of 0.2 to 0.6 mm, preferably in the range 0.24 to 0.47 mm, most preferably 0.28 to 0.35 mm.

The invention will be illustrated by the following Examples.

Materials used:

α-lactose monohydrate supplied under the trade designation Pharmatose 325M by DMV International Pharma was micronised by fluid energy milling in a single pass (referred to here and in the following as "micronised lactose monohydrate"). Micronised lactose monohydrate (100 g) was dispersed in Anhydrous Ethanol (840 g) using a Silverson high shear mixer. This dispersion was added to the product reservoir of an Avestin Emulsiflex C50 homogenizer, and recirculated for 20 minutes at 10,000 psi. The dispersion was then passed out of the homogenizer, after recirculation for 30 seconds, at 20,000 psi. The particle size was determined according to the following method.

Particle Size Analysis

For analysis of a Lactose/Ethanol slurry, a (0.5 ml) sample of the slurry, which was shaken for at least one minute to ensure homogeneity, was added to a solution of 0.05% Lecithin in Iso-octane (20 ml), and redispersed with mild ultrasonics for 1 minute.

The resulting suspension was introduced dropwise into the presentation cell (a Hydro 2000 SM small sample presentation cell) of a Malvern Mastersizer 2000™ laser diffraction particle sizer until the obscuration was in the working range (between 10 and 12 with a red laser), and left to circulate for 1 minute to allow complete mixing and thermal equilibrium to be established. Ten readings were taken at 20 second intervals to establish that the particle size was stable. The General Purpose analysis model, as described in the Malvern Instruments Operators Guide, was used with refractive indices 1.533 (lactose), 1.392 (iso-octane) and absorbance 0.001 (lactose). The results are based on the average calculated results of 10 readings taken in succession. The procedure was performed twice.

Results of Particle Size Analysis by Malvern Mastersizer 2000

	Lactose
Units	Microns
d(v,0.1)	0.073
d(v,0.5) median	0.170
d(v,0.9)	1.259
D[4,3] volume weighted mean	0.455
Units	Percent
vol under 0.05 micron	2.10
vol under 0.10 micron	23.10
vol under 0.20 micron	57.48
vol under 0.50 micron	76.49
vol under 1.0 micron	86.56
vol under 2.0 micron	95.97
vol under 5.0 micron	99.54
vol under 10.0 micron	100.00
vol under 20.0 micron	100.00

5

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/US 03/10285

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/12 A61K9/70 A61K31/58 A61K31/167 A61K47/10
A61K47/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 47286 A (JINKS PHILIP A ;OLIVER MARTIN J (GB); PALING SIMON G (GB); JAISWAL) 18 December 1997 (1997-12-18) cited in the application the whole document page 4, line 12 -page 6, line 25 claims 1-23	1-15
Y	WO 98 52542 A (MULLER HELGERT ;FATANIA KANU M (GB); OLIVER MARTIN J (GB); SCOTT J) 26 November 1998 (1998-11-26) cited in the application the whole document page 3 page 12, line 3-10; examples 13-16 claims 1-19	1-15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 July 2003	06/08/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Luangkhot, N

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 03/10285

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 65464 A (BOEHRINGER INGELHEIM PHARMA) 23 December 1999 (1999-12-23) cited in the application the whole document claims 1-10,14,20	15
A	DE 195 41 689 A (BYK GULDEN LOMBERG CHEM FAB) 15 May 1996 (1996-05-15) cited in the application the whole document	1
A	WO 99 65460 A (BAKER NORTON PHARMA) 23 December 1999 (1999-12-23) the whole document	1

INTERNATIONAL SEARCH REPORT

ation on patent family members

Internal application No
PCT/US 03/10285

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9747286	A	18-12-1997	AU	726382 B2	02-11-2000
			AU	3373997 A	07-01-1998
			CA	2257841 A1	18-12-1997
			EP	0934057 A1	11-08-1999
			JP	2000513340 T	10-10-2000
			NO	985720 A	11-02-1999
			NZ	333202 A	23-06-2000
			US	6054488 A	25-04-2000
			WO	9747286 A1	18-12-1997
			ZA	9704546 A	23-11-1998
WO 9852542	A	26-11-1998	AU	726835 B2	23-11-2000
			AU	7496298 A	11-12-1998
			BG	103902 A	31-05-2000
			BR	9809448 A	20-06-2000
			CN	1257421 T	21-06-2000
			EA	2381 B1	25-04-2002
			EP	0983058 A1	08-03-2000
			HU	0002691 A2	28-02-2001
			JP	2001526685 T	18-12-2001
			NO	995667 A	18-11-1999
			NZ	500874 A	28-09-2001
			PL	336885 A1	17-07-2000
			SK	157699 A3	16-05-2000
			TR	9902863 T2	22-05-2000
			US	6120752 A	19-09-2000
			WO	9852542 A1	26-11-1998
WO 9965464	A	23-12-1999	DE	19827178 A1	27-04-2000
			DE	19842963 A1	23-03-2000
			AU	759222 B2	10-04-2003
			AU	4552199 A	05-01-2000
			BG	105033 A	28-09-2001
			BR	9911351 A	13-03-2001
			CA	2335065 A1	23-12-1999
			CN	1307470 T	08-08-2001
			EE	200000759 A	15-04-2002
			EP	1087750 A1	04-04-2001
			HR	20000867 A1	31-10-2001
			HU	0104734 A2	29-05-2002
			NO	20006318 A	30-01-2001
			NZ	509418 A	30-06-2003
			PL	345685 A1	02-01-2002
			SK	19392000 A3	10-07-2001
			TR	200003721 T2	21-06-2001
			WO	9965464 A1	23-12-1999
			ZA	200007581 A	02-04-2002
DE 19541689	A	15-05-1996	DE	19541689 A1	15-05-1996
WO 9965460	A	23-12-1999	US	2002018753 A1	14-02-2002
			AU	762927 B2	10-07-2003
			AU	4825999 A	05-01-2000
			BR	9912170 A	23-10-2001
			CA	2335303 A1	23-12-1999
			CN	1310611 T	29-08-2001
			EP	1306082 A1	02-05-2003
			EP	1085856 A2	28-03-2001

INTERNATIONAL SEARCH REPORT

lation on patent family members

Internat Application No
PCT/US 03/10285

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9965460 A		HU 0102468 A2	28-03-2002
		JP 2002518100 T	25-06-2002
		NO 20006466 A	16-02-2001
		PL 345399 A1	17-12-2001
		SK 19442000 A3	11-09-2001
		WO 9965460 A2	23-12-1999
		US 2003077230 A1	24-04-2003